REMARKS

Reconsideration is requested. The status of the claims is as follows:

Original:	None
Previously presented:	1 and 48-64
Canceled:	2-47
New:	65-68

Claims 2-47 were canceled previously. Claims 65 to 68 are new. Claims 1 and 48-68 are pending with entry of this amendment.

New claims 65 to 68 recite that efavirenz is present in an amount of either 300 mg or 600 mg, support for which can be found, for example, on page 2, lines 21-22 of the specification. The new claims do not introduce new matter.

Rejection under 35 U.S.C. § 103

Claims 1 and 48-64 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Makooi in view of Remington or Phipps (US 5,260,073). This rejection is traversed with respect to all of the claims. (Note: The inclusion of claim 56 in this rejection is believed to be an inadvertent error, since the Examiner concluded elsewhere in the Office Action that claim 56 constituted allowable subject matter. To the extent claim 56 is included in this rejection, however, the arguments set forth below in response to this rejection apply thereto.)

For the reasons given in the responses filed October 6, 2003 and September 7, 2004 and incorporated by reference herein, it is Applicants' position that Makooi does not teach or suggest the use of a low level of superdisintegrant in efavirenz formulations, whether considered alone or in view of Remington. Quite the contrary, Makooi in view of Remington clearly directs the person of ordinary skill in the art to employ 10 wt.% or more of superdisintegrant.

Phipps also fails to cure the deficiencies of Makooi. Phipps is directed to the use of l(-)- and d(+)-norephedrine, alone or in combination, as mucosecretory agents. Phipps discloses that l(-)norephedrine can be orally administered in the form of a tablet (col. 7, line 18) and particularly discloses a tablet that contains, *inter alia*, a disintegrant and a binder (col. 8, lines 39-44). However, Phipps is not directed to HIV antivirals and does not teach or suggest efavirenz or efavirenz-containing compositions. There is no motivation to combine Phipps with Makooi, and, even if it were combined, the combination would direct the skilled artisan to employ 10 wt.% or more of superdisintegrant in efavirenz-containing compressed tablet compositions.

The Examiner has admitted that Makooi does not teach a 1-5 wt.% superdisintegrant concentration, but has asserted that it would be obvious for the person of ordinary skill in the art of dosage formulation to optimize the Makooi dosage forms to improve the pharmacokinetic characteristics of Makooi's dosage formulation (Office Action, last paragraph on page 4). It is Applicant's position that optimization of the teachings of Makooi cannot lead the person of ordinary skill in the art to an efavirenz-containing tablet composition having a 1-5 wt.% superdisintegrant concentration, because Makooi teaches compositions having 10 wt.% or more superdisintegrant.

The Examiner has asserted that the scope of the instant claims is not limited to 1-5 wt.% superdisintegrant because the distinction between disintegrants and superdisintegrants is illusory; i.e., the Examiner asserts that neither the specification nor the art draws a distinction between the scope of disintegrants and superdisintegrants. Applicant disagrees. The specification expressly refers to disintegrants and superdisintegrants and discloses compositions that include disintegrants and superdisintegrants as separate and distinct components. The presence of both terms in the specification and their use to define and describe different components demonstrates that the specification draws a distinction between the terms. Indeed, it would be pointless to include both terms in the specification if there were no distinction between them. Furthermore, it is well-recognized in the art that superdisintegrants are a subset of disintegrants. Remington, for example, discloses (p.1637, bottom of first column) that a "new group of materials known as 'super disintegrants' have gained in popularity as disintegrating agents." As another example, Thibert et al., J. Pharm. Sci. 1996, 85(11): 1255-1258 (copy enclosed) describes superdisintegrant hydration studies using environmental scanning electron spectroscopy, and specifically discloses that croscarmellose sodium, crospovidone, and sodium starch glycolate are superdisintegrants. As noted by the Examiner, Phipps does not distinguish between disintegrants and superdisintegrants. However, Phipps' failure to make this distinction does not mean the distinction does not exist, but instead means that the distinction is not important in the context of Phipps' tablet formulations. Interestingly, while not expressly identified as superdisintegrants, all of Phipps' particularly preferred disintegrants are in fact art-recognized superdisintegrants (col. 8, lines 62-64).

The Examiner has asserted that the description at lines 21-27 on page 3 of the specification is an inclusive description of superdisintegrants, not an exclusive one, and characterizes Applicant's explanation of lines 21-27 in the response filed September 7, 2004 (and incorporated herein by reference) as an attempt to narrow the scope of the term superdisintegrant that amounts to the constructive addition of new matter. Applicant disagrees. The presence of the terms disintegrant and superdisintegrant in the specification and the fact that the specification and the claims (including the original claims) recite a "filler/disintegrant" and a "superdisintegrant" as separate and distinct components of the tablet formulation of the invention demonstrates that the terms must differ in scope. Lines 21-27 are consistent with this difference

in the scope of the terms in that the lines state that certain of the disintegrants listed at lines 8-13 are superdisintegrants. To construe lines 21-27 to mean that superdisintegrants and disintegrants are to be used interchangeably and without distinction is inconsistent with and not supported by the rest of the specification. Accordingly, both the specification and the art recognize superdisintegrants as a special class of disintegrants.

The Examiner has also asserted that Makooi does not teach away from the instantly claimed compositions containing 1-5 wt.% superdisintegrant. Applicant disagrees. Makooi directs the skilled artisan to employ 10 wt.% or more of a superdisintegrant. Accordingly, any optimization of the amounts of superdisintegrant based upon the teachings of Makooi would necessarily lead to a formulation containing at least 10 wt.% superdisintegrant, and thus Makooi clearly teaches away from the claimed compositions containing 1-5 wt.% superdisintegrant.

Withdrawal of the rejection under section 103 is requested in view of the foregoing remarks.

Declaration under 37 C.F.R. 1.132

Assuming strictly for the sake of argument that the claims were prima facie obvious, then the claims are patentable over Makooi and Remington or Phipps in view of the unexpected results set forth in the Rule 132 Declaration of Munir Alwan Hussain (hereinafter the "Declaration") that accompanied the response filed October 6, 2003. The Declaration presents the results of several pharmacokinetic studies involving efavirenz tablets and capsules. These studies were bioequivalency studies that were part of the effort at DuPont Pharmaceutical Company (since acquired and now part of Bristol-Myers Squibb Pharma) to develop an efavirenz compressed tablet that was bioequivalent to the commercial capsule formulation of efavirenz. These studies demonstrated that tablets prepared in accordance with Makooi (i.e., tablets containing 50 or 60 wt.% efavirenz and 10 wt.% or more superdisintegrant) had less bioavailability than (and thus were not bioequivalent to) efavirenz commercial capsules, whereas the tablets of the claimed invention (i.e., tablets containing 50 wt.% efavirenz and 4 or 5 wt.% superdisintegrant) had the same (i.e., were bioequivalent to) or better bioavailability than the capsules. This result is neither taught nor suggested by Makooi in view of Remington or Phipps. Furthermore, per the Declaration, it is also noted that, absent the development of a tablet bioequivalent to the commercial capsule, a full scale clinical trial with a non-bioequivalent tablet is required to demonstrate the tablet's safety and efficacy. Conducting a full scale clinical trial is costly in terms of time and resources and can also substantially delay approval and launch. The claimed invention resulted in the development of an FDA-approved bioequivalent tablet without the need for a full scale clinical trial, a benefit not achieved via the Makooi invention. Clearly then, under the assumption that the claimed invention is prima facie obvious over the cited references (which it is not), the Declaration provides evidence of unexpected results rebutting the alleged prima facie case.

The Examiner has asserted that the Declaration is sufficient to overcome the rejection of claim 56 but is not commensurate in scope with the other claims. Claim 56 recites a tablet composition containing specific ingredients in specific amounts, and corresponds to one of the tablet compositions used in the experiments described in the Declaration. The Examiner's interpretation of the results set forth in the Declaration is unreasonably narrow. It is Applicants' position that the evidence of unexpected results provided in the Declaration can be extrapolated to and is representative of the entire class of tablets embraced by the claims as amended herein. The Declaration shows that efavirenz tablets containing 50 wt.% efavirenz and 4 or 5 wt.% or less of superdisintegrant unexpectedly have better bioavailability than comparable tablets having 50 or 60 wt.% efavirenz and 10 wt.% or more superdisintegrant and unexpectedly have comparable or better bioavailability than commercial capsules. This showing supports the patentability of all of the claims in that each claim recites a tablet containing about 50 wt.% efavirenz and about 1-5 wt.% of a superdisintegrant.

Claim Objection

Claim 56 has been objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form. The Examiner's invitation to rewrite the claim in independent form is declined, because it is believed that the rejection of the base claim should be withdrawn for the reasons set forth above. Withdrawal of the objection is accordingly requested.

Recommendations

The Examiner has recommended that "generic claims 1 and 57 be limited to the specific disintegrants and superdisintegrants to the extent they exclude each other." (Office Action, page 8) It is respectfully noted that claims 52-55 and 62-64 (and new claims 65 to 68 as well) comply with this recommendation (i.e., in each of these claims the superdisintegrant is croscarmellose sodium and the filler/disintegrant is microcrystalline cellulose), but they nonetheless stand rejected. It is further noted that, since these claims recite a specific disintegrant and a specific superdisintegrant, the distinction between disintegrants and superdisintegrants in these claims is clearly not illusory. Accordingly, it is believed that claims 52-55 and 62-64 (and new claims 65 to 68) constitute allowable subject matter.

Interview Summary

The undersigned and Examiner Sharareh participated in a series of short (~ 5 minutes or less) telephonic interviews on December 15 and 23, 2004 and on January 3, 6 and 7, 2005, hereinafter collectively referred to as the "interview". The claims under discussion were 52-55 and 62-64, especially claim 52. No exhibit was shown and no demonstration was conducted. In the December 2004 portion of the interview, the undersigned initially pointed out to the Examiner that claims 52-55 and 62-64 complied with the recommendation set forth on page 8 of the Office Action, thus the distinction between disintegrants and superdisintegrants in these

claims is not illusory, and thus the rejection of these claims should be withdrawn. The Examiner acknowledged that these claims comply with the recommendation, but was nonetheless not convinced the claims constituted allowable subject matter, in response to which the undersigned reviewed the reasons these claims were patentable over Makooi in view of Remington and/or Phipps, which reasons were the same as those set forth in more detail both hereinabove and in the communication filed on September 7, 2004. No agreement was reached on the patentability of these claims.

The discussion during the January 2005 portion of the interview focused on the Rule 132 Hussain Declaration filed October 6, 2003. The discussion centered on whether or not the data in the Declaration (notably the PK results for Study A as compared to the PK results for Study C) is evidence of unexpected results with respect to the formulations set forth in claims 52-55 and 62-64, wherein the undersigned believed the Declaration constitutes a showing of unexpected results, but the Examiner was not entirely convinced. No agreement was reached. The Examiner suggested that Applicant submit the results of a PK study analogous to Study C, wherein tablets as set forth in Example 3 of Makooi are compared to tablets of the claimed invention such as those employed in Study C, D or E in the Declaration.

No other issues were discussed.

The application is believed to be in condition for allowance and passage to issue is requested. The Examiner is invited to telephone the undersigned should any minor matters need to be resolved before a Notice of Allowance can be mailed.

Respectfully submitted,

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Direct Visualization of Superdisintegrant Hydration Using Environmental Scanning Electron Microscopy

To the Editor:

The mechanisms of action of pharmaceutical superdisintegrants have been studied by many groups over the last decade, and swelling and wicking of water have been proposed as their primary modes of action.[1–3] Both the extent and rate of disintegrant swelling upon immersion in water have been related to tablet disintegration,[4] but neither of these factors appears to be uniquely responsible for the disintegration process. Disintegrating force development has also been proposed as a factor, and the efficiency of some superdisintegrants may be related to their high rate of water uptake through a wicking mechanism.[5] The hydration of superdisintegrants has been studied using techniques such as optical microscopy,[6,7] electrical zone sensing (Coulter counter),[8] and video recording.[9] Each of these techniques involves examining the particles under some form of constraint (*e.g.*, ionic strength for the Coulter counter and mechanical constraint (a glass cover slide) for optical microscopy and video recording). These constraints may alter the hydration behavior of the disintegrant particles when exposed to an aqueous environment. In order to minimize the effects of such constraints we have directly observed the hydration behavior of several superdisintegrant powders using an environmental scanning electron microscope (ESEM). The results of these studies are described in this Communication.

Three types of superdisintegrant were investigated, croscarmellose sodium (Ac-Di-Sol, FMC Corp.), crospovidone Kollidon CL, BASF Corp.), and sodium starch glycolate Explotab, Edward Mendell Co., Inc.), and each was used as received. Sodium chloride (analytical grade) and microcrystalline cellulose (Avicel PH101, FMC Corp.) were examined as reference materials.

A calibrated dynamic moisture balance (MB-300G, VTI Corp., Hialeah, FL) was used to evaluate the moisture sorption characteristics of the materials at a range of relative humidities. A conventional scanning electron microscope SEM) (JSM-820, Jeol Corp., Peabody, MA) was used for preliminary observation of the superdisintegrants. An Oxford Cryostage (model Cryotrans, Oxford Instruments, Oxford, U.K.) attached to a side port of the JSM-820 was used for cryo-SEM studies of the materials. An ESEM (model 2010, ElectroScan Corp., Wilmington, MA) was used to observe the superdisintegrants when exposed to controlled amounts of water vapor. This instrument allows visualization of samples without the usual coating procedure associated with standard SEM, and under varying water vapor pressures. The principles used in the imaging of the materials are similar to those of conventional SEM. The difference lies in the use of a differential-vacuum pumping system and pressure-limiting orifices to create a controlled-pressure water vapor environment. Before the ESEM experiments were started, the accuracy of the relative humidity (RH) control in the chamber was tested by observation of the deliquescence of sodium chloride crystals. This occurred at about 8.8 Torr, which corresponds to 70% RH at 15 °C (Figure 1). This is close to the reported literature value of 75% RH and confirms the accurate control of water vapor pressure and temperature in the ESEM chamber.

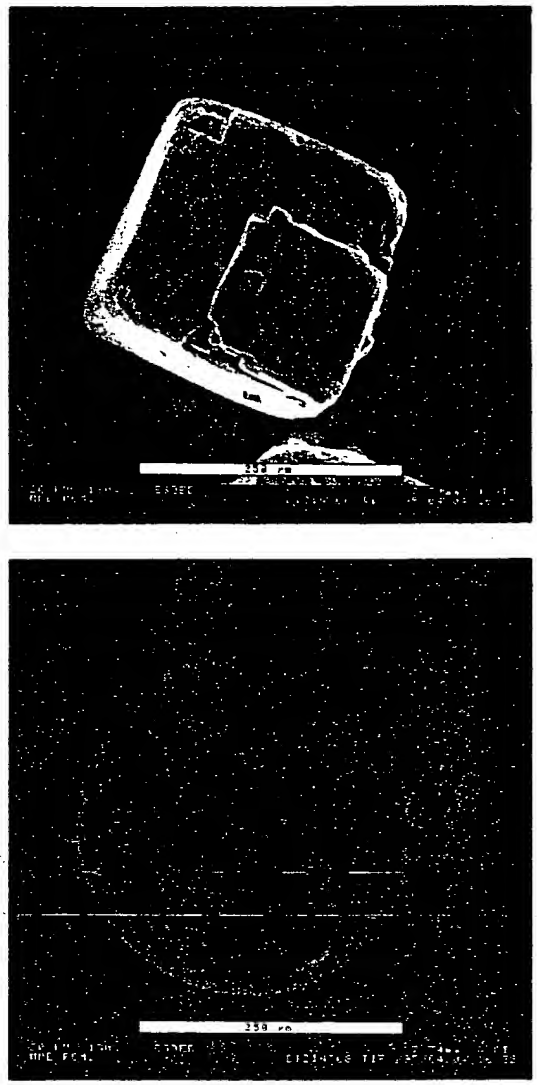

Figure 1—Sodium chloride crystal (a, top) initially at 40% RH/15 °C and (b, bottom) undergoing deliquescence at 75%RH/15 °C.

The dynamic water vapor sorption experiments indicated that the maximum amount of water vapor sorbed at 90% RH for the different superdisintegrant samples varied between 48% w/w for croscarmellose sodium to 62% w/w for sodium starch glycolate (Figure 2a–c). Sodium starch glycolate and crospovidone showed minimal hysteresis in their water vapor sorption–desorption curves, as opposed to a marked hysteresis observed for the croscarmellose sodium sample. There was no evidence of macroscopic morphological changes in any of the specimens during or after the water vapor sorption experiments, except for a worsening of the flow properties of the powders stored at high humidity.

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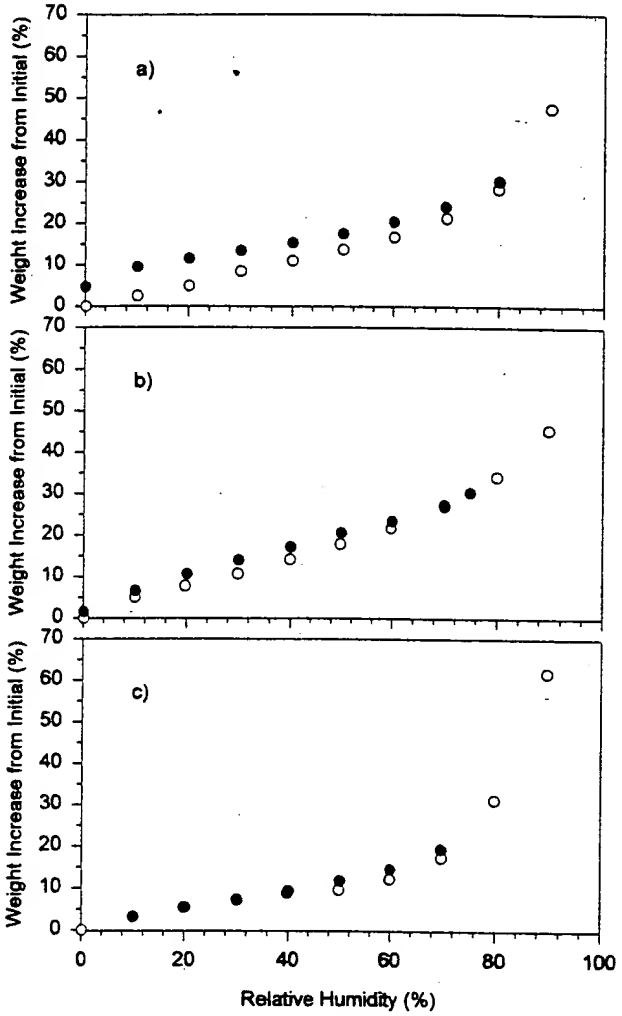

Figure 2—The water vapor sorption (○) and desorption (●) isotherms for (a) croscarmellose sodium, (b) crospovidone, and (c) sodium starch glycolate.

Several samples of the superdisintegrants were equilibrated at a relative humidity of 92% RH at 30 °C (using a saturated solution of potassium nitrate in a desiccator) for a period of 1 week and examined by conventional SEM and cryo-SEM. There were no noticeable differences in the morphology andstructure of these samples compared to similar samples stored under ambient conditions. The lack of any morphological differences after storage at high relative humidities was unexpected[5,9] and inconsistent with the observed water vapor sorption behavior. If water was placed directly on the samples, followed by rapid freezing in the cryo-SEM, morphological and surface changes were observed for all three superdisintegrants. These included swelling, untwisting, and fusion of the particles (not shown). This illustrates some of the problems associated with using conventional high-vacuum SEM methods for observing hydrated pharmaceutical materials. It appears that dehydration of samples in a regular SEM can be very rapid, even under low temperature (cryogenic) conditions, and this can prevent direct observation of hydrated specimens.

Direct visualization of the hydration behavior of the superdisintegrants was made by observing uncoated samples in the ESEM. The water vapor pressure was initially set at 4.9 Torr, which corresponds to a relative humidity of approximately 40% at 15 °C. The samples were allowed 5 min to equilibrate in this environment. The water vapor pressure was then increased gradually to 10 torr (80% RH at 15 °C), and the samples were allowed 5 min to equilibrate. The last step was to slowly lower the relative water vapor pressure back to 4.9 Torr to partially dehydrate the samples. This range of relative humidities was chosen to represent the likely humidities experienced by the superdisintegrants during normal pharmaceutical storage and processing operations. At 40% RH the croscarmellose sodium particles comprised twisted fibers approximately 180 μm in length and 25 μm in diameter (Figure 3a). Upon exposure to 80% RH the particles experienced considerable twisting and expansion (Figure 3b). These modifications were visualized in real time as the relative humidity in the chamber increased. After the relative humidity was reduced to 40%, the particles did not regain their original shape (Figure 3c), and this may be linked to the hysteresis observed in the water vapor sorption isotherm for this material (Figure 2a). The sodium starch glycolate particles initially comprised oblate particles approximately 40 μm in diameter (Figure 4a). Upon exposure to an elevated relative humidity (80% RH) the particles experienced swelling and deformation (Figure 4b). Fusion of particles was also observed, and this caused irreversible changes in the structure of the material even after reduction of the relative humidity to 40%. Some shrinkage of the fused material was observed on dehydration/drying (Figure 4c). In contrast to the croscarmellose, the water vapor sorption isotherm for the sodium starch glycolate showed no sorption–desorption hysteresis over this range of relative humidities (Figure 2b) despite the obvious structural changes that were taking place in the sample. In the case of crospovidone, the material comprised highly tortuous particles resembling crumpled pieces of paper as previously reported.[10] There were very few signs of swelling even after prolonged exposure to 80% RH, and the particles maintained their physical integrity upon dehydration and repeated hydration–dehydration cycling (not shown). The surface aspects and morphology of the particles were not noticeably changed even when observed at high magnification. The effect of changing relative humidity on the morphology of particles of microcrystalline cellulose, a widely used pharmaceutical tabletting excipient, was also determined. There were no observable changes in the particle morphology nor was there any swelling of the microcrystalline cellulose particles after prolonged exposure to a relative humidity of 80%. These results are consistent with the limited disintegrant properties of this material[10] and its lower reported level of water vapor sorption.[11]

Conclusions—The morphological properties of pharmaceutical materials in their near native states can be readily determined as a function of relative humidity and temperature using environmental scanning electron microscopy. Other advantages of ESEM include greater resolution, increased depth of field, and higher magnification compared to light microscopy, and the lack of the potentially destructive sample preparation techniques required for conventional SEM observation. ESEM has been used to directly observe the hydration behavior of several materials used as superdisintegrants in pharmaceutical tablet formulations. The technique provided direct visual confirmation of the importance of swelling as a mechanism of action for two commercially available superdisintegrants, croscarmellose sodium and sodium starch glycolate. Additionally, it indicated that crospovidone does not undergo any large degree of swelling during hydration in its native state. Other modes of action (*e.g.*, wicking) could not be directly confirmed; however, it was

Figure 3—Croscarmellose sodium particles (a, top) at 40% RH/15 °C, (b, middle) at 80% RH/15 °C, and (c, bottom) after "drying" at 40% RH/15 °C.

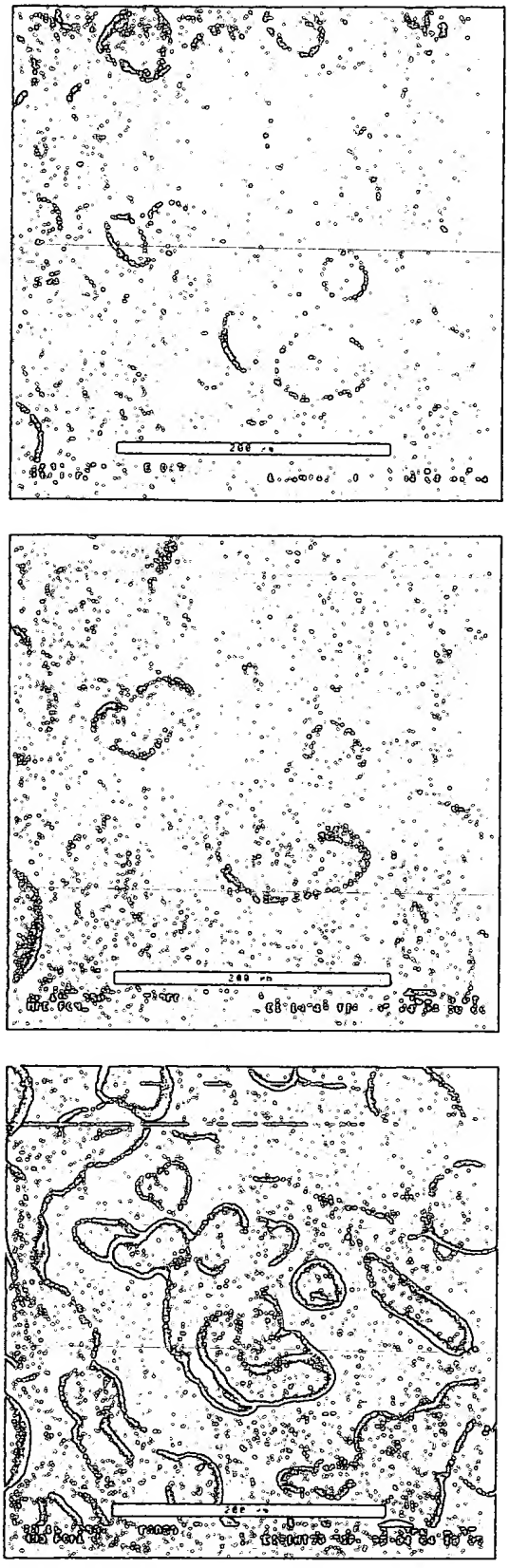

Figure 4—Sodium starch glycolate particles undergoing hydration (a, top) at 40% RH/15 °C, (b, middle) at 80% RH/15 °C, and (c, bottom) after "drying" at 40% RH/15 °C.

observed that the morphological changes for each material were unique, suggesting different modes of superdisintegrant action for each excipient. Following this initial feasibility study we plan to develop image analysis techniques to quantify the morphological changes that have been observed and to study the effects of processing (*e.g.*, compression, milling) on the hydration behavior of pharmaceutical superdisintegrants.

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